J Shoulder Elbow Surg (2019) 28, 304–309

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

Association of steroid injection with soft-tissue calcification in lateral epicondylitis

Hyung Bin Park, MD, PhD*, Mincheol Kam, MD, Ji-Yong Gwark, MD

Department of Orthopaedic Surgery, Gyeongsang National University School of Medicine and Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

Background: Steroid injections are among the most commonly used conservative treatments for lateral epicondylitis (LE). Although soft-tissue calcification has been reported as a steroid injection complication in certain tendons, such an association in LE has not been established. This study's purpose was to determine any association of both a history of steroid injection and the number of steroid injections with the types of calcification found in LE.

Methods: This study included 110 patients (110 elbows) with LE diagnosed from February 2016 to October 2017. We categorized calcifications seen on standard elbow radiographs as soft-tissue calcifications or enthesophytes using the classification of Shillito et al. Using logistic regression analyses, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for various factors possibly affecting calcification in LE: age, sex, body mass index, dominant-side involvement, occupation, symptom duration, hand-grip power, pain score on a visual analog scale, and treatment methods. The evaluated treatments included stretching exercise, extracorporeal shockwave therapy, and steroid injections.

Results: In the univariate analysis, the visual analog scale pain score, a history of steroid injection, and the number of steroid injections were significantly associated with soft-tissue calcification ($P \leq .020$). In the multivariable analysis, a history of steroid injection (OR, 7.63; 95% CI, 1.63-35.72) and the number of steroid injections (OR, 1.18; 95% CI, 1.06-1.32) were significantly associated with soft-tissue calcification ($P \leq .010$).

Conclusions: The significant association of steroid injections with soft-tissue calcification in LE suggests that this calcification is likely to be an iatrogenic complication of steroid injection.

Level of evidence: Level III; Case Control Design; Treatment Study

Keywords: Lateral epicondylitis; soft-tissue calcification; steroid injection; Complication; Conservative treatment; Enthesophyte

Lateral epicondylitis (LE) is one of the most common diseases that cause elbow pain.[23] The incidence of LE is estimated at 4 to 7 per 1000 patients per year in general practice[11,22] and between 1% and 3% per year in the general population.[1,5,6,14] The prevalence of LE has been reported as 1.3% to 12.2%.[13,20] The radiologic findings of LE are nonspecific or normal. However, the most common radiologic finding is calcification at the lateral epicondyle. The reported prevalence of calcification in LE has ranged from 7% to 47% based on the

Approval was received from the Institutional Review Board of Gyeongsang National University Changwon Hospital (No. GNUH 2018-01-002-001).

*Reprint requests: Hyung Bin Park, MD, PhD, Department of Orthopaedic Surgery, Gyeongsang National University, Changwon Hospital, 11 Samjeongjaro, Changwon, Republic of Korea, 51472.

E-mail address: hbinpark@gnu.ac.kr (H.B. Park).

1058-2746/$ - see front matter
https://doi.org/10.1016/j.jse.2018.10.009

studied groups.[15,17,19] In most patients, LE can be treated successfully with conservative treatments. Steroid injection is one of the most commonly used interventions for LE. A systematic therapeutic overview has showed that 14% to 38% of patients with LE were treated with corticosteroid injections.[3] In case reports of plantar fasciitis and LE, soft-tissue calcification has been reported as a complication after steroid injection.[7,9,10,18] However, we have found no report of any analysis using statistical methods to determine any association between soft-tissue calcification and LE. Nirschl[15,16] mentioned that multiple cortisone injections or tendon calcifications are factors to be considered in choosing a surgical treatment of LE. Nirschl suggested that tendon calcification represents a pathologic tendon, distinct from lateral epicondylar exostoses (enthesophytes). However, we are aware of no further study that supports this suggestion. Whether steroid injection is associated with soft-tissue calcification in LE is yet to be completely determined. The purpose of this study was to determine any association of both a history of steroid injection and the number of steroid injections with the types of calcification found in LE.

Materials and methods

We performed a retrospective review of all new patients who received a diagnosis of LE by a single orthopedic surgeon (H.B.P.) from February 2016 to October 2017. LE was diagnosed based on the following symptoms and signs observed during physical examinations: (1) pain located at the lateral aspect of the elbow, (2) point tenderness over the lateral epicondyle, and (3) pain during resistive dorsiflexion of the wrist with the elbow in full extension.[12] This study included 110 elbows in 110 patients with a diagnosis of LE. Among those patients, 16 received a diagnosis of bilateral involvement. In cases of unequal bilateral involvement, the more symptomatic side was selected (12 patients). In cases in which the patients' sides had similar symptoms (4 patients), one side was selected using the random number generator function of Microsoft Excel (Office 2016; Microsoft, Redmond, WA, USA). Age, sex, body mass index, dominant-side involvement, occupation, symptom duration, hand-grip power, pain score on a visual analog scale (VAS), and treatment methods were recorded. The evaluated treatment methods were nonsteroidal anti-inflammatory drug treatment, opioid treatment, stretching exercise, extracorporeal shockwave therapy, and steroid injection. We also reviewed whether steroid injections had been used alone or with any local anesthetics.

The prevalence, among the studied patients, of a history of steroid injections was 53.6% (59 of 110 patients). Of the patients, 34.5% (38 of 110) had been treated with both a steroid and 1 local anesthetic, which was lidocaine; 19.1% (21 of 110) had been treated with a steroid without any local anesthetic. The steroid used was triamcinolone. The mean number of steroid injections was 3.0 among all patients and 6.4 in the soft-tissue calcification group. Table I summarizes the studied variables according to the type of calcification.

We evaluated standard elbow radiographs (anteroposterior, lateral, and internal and external oblique views) and recorded the types of calcification around the lateral epicondyles. We classified calcifications as enthesophytes and soft-tissue calcifications according to

Table I Summary of studied variables according to studied groups

Studied variable	All patients (n = 110)	Overall calcification (n = 38)	Enthesophyte (n = 20)	Soft-tissue calcification (n = 18)
Age, yr	50.0 ± 9.7	52.2 ± 8.5	51.5 ± 7.6	52.9 ± 9.8
Male sex	46.4%	42.1%	40.0%	44.4%
BMI, kg/m^2	24.2 ± 4.3	24.6 ± 3.1	25.0 ± 3.3	23.2 ± 3.0
Dominant-side involvement	78.2%	79.0%	90.0%	66.7%
Occupation				
Office worker	24.5%	26.3%	20%	33.3%
Manual laborer	46.4%	44.7%	50%	38.9%
Housewife	29.1%	29.0%	30%	27.8%
Symptom duration, mo	11.2 ± 15.2	13.5 ± 16.7	13.5 ± 20.9	13.6 ± 11.7
Hand-grip power, kg	24.9 ± 11.3	25.5 ± 7.2	25.9 ± 8.3	25.3 ± 5.9
NSAID treatment	100%	100%	100%	100%
Opioid treatment	84.5%	92.0%	85.0%	100%
Stretching exercise	70.0%	78.9%	75.0%	77.8%
ESWT	22.7%	21.1%	25.0%	16.7%
VAS pain score	5.9 ± 2.0	6.7 ± 1.5	6.5 ± 1.3	6.9 ± 1.8
History of steroid injection	53.6%	73.7%	60.0%	88.9%
With local anesthetic	34.5%	36.8%	35.0%	33.3%
Without local anesthetic	19.1%	36.8%	25.0%	55.6%
No. of steroid injections	3.0 ± 4.4	4.8 ± 5.1	3.3 ± 3.8	6.4 ± 6.0
With local anesthetic	3.34 ± 3.01	4.6 ± 3.8	3.5 ± 1.9	6.7 ± 4.2
Without local anesthetic	2.63 ± 2.91	5.1 ± 2.3	3.1 ± 2.3	6.0 ± 5.2

BMI, body mass index; *NSAID*, nonsteroidal anti-inflammatory drug; *ESWT*, extracorporeal shockwave therapy; *VAS*, visual analog scale.
Data are presented as mean ± standard deviation or percentage.

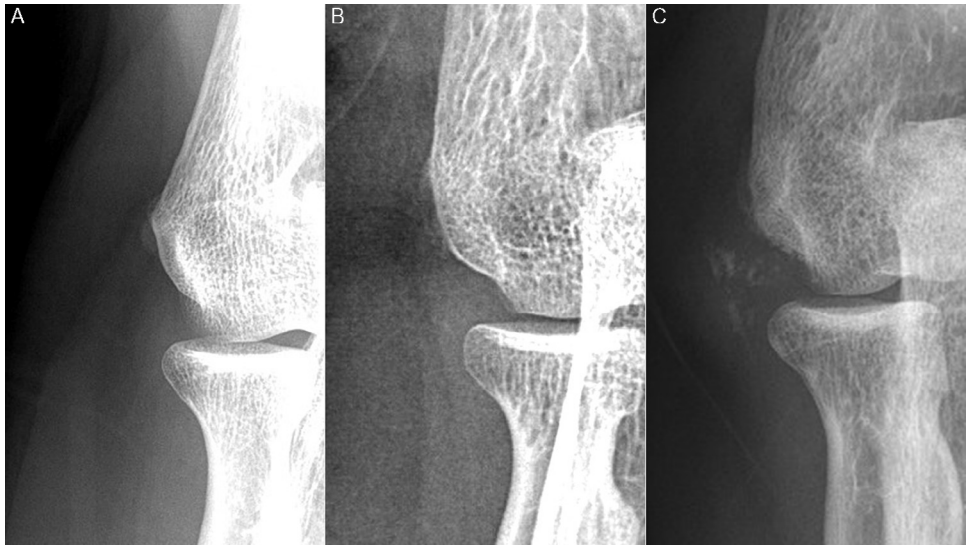

Figure 1 Calcifications around lateral epicondyle. **(A, B)** Enthesophyte, with calcification directly in contact with bone. **(C)** Soft-tissue calcification, with calcification separate from bone.

the classification of Shillito et al[19] (Fig. 1). Type A was defined by calcification directly in contact with the bone. Type A was further divided into types A1 and A2, depending on the size, relative to the distance from the apex to the most distal extent of the epicondyle. Involvement of less than 50% of this distance was classified as type A1, whereas involvement of 50% or more was classified as type A2. Type B, a soft-tissue calcification, was defined by calcification separate from the bone. Any abnormal radiographic finding other than calcification around the lateral epicondyle was evaluated. We evaluated the radiographs during the initial visits and the final follow-up visits to assess whether the patients' symptoms had worsened. All the patients' initial radiographs had shown no soft-tissue calcification.

The hand-grip power measurement was conducted according to standard procedures recommended by the American Society of Hand Therapists,[8] using the Jamar Plus+ Digital Hand Dynamometer (Patterson Medical, Warrenville, IL, USA).

The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to identify any association between various studied factors and calcification in LE, using univariate logistic regression analysis. Then, we performed a multivariable logistic regression analysis, using only the significant variables that had resulted from the univariate analysis. Multivariable logistic regression analysis was performed after assessment of multicollinearity, using factors with a variance inflation factor and a condition index. We considered both a variance inflation factor and a condition index of less than 10 to be among the variables indicating absence of multicollinearity.[4] The Hosmer-Lemeshow test was used to determine the goodness of fit for the multivariable logistic regression model. All statistical analyses were performed with the SPSS software program (IBM SPSS Statistics for Windows, version 21.0; IBM, Armonk, NY, USA). The significance of the logistic regression analysis was set at $P < .05$. The significance of the Hosmer-Lemeshow test was set at $P > .05$.

Results

The overall prevalence of calcification in LE was 35.5% (38 of 110 patients). Among these LE patients, 18.2% (20 of 110) had enthesophytes and 16.4% (18 of 110) had soft-tissue calcifications. The most common radiographic finding other than calcification around the lateral epicondyle was olecranon enthesophytes (11.8%, 13 of 110). The prevalence of radiographic findings other than calcification is summarized in Table II.

In the univariate logistic regression analysis, the initial VAS pain score, a history of steroid injection, and the number of steroid injections were significantly associated with overall calcification. No studied variables had any significance with enthesophytes. Among the studied variables, the initial VAS pain score, a history of steroid injection, and the number of steroid injections were significantly associated with soft-tissue calcification. The ORs with 95% CIs for all variables are summarized in Table III.

In the multivariable analyses, the initial VAS pain score, a history of steroid injection, and the number of steroid injections were significantly associated with overall calcification. Among the studied variables, a history of steroid injection and the number of steroid injections were significantly

Table II Radiographic findings in lateral epicondylitis patients

Radiographic finding	Prevalence, %
Overall calcification around lateral epicondyle	34.5 (38 of 110)
Enthesophyte	18.2 (20 of 110)
Soft-tissue calcification	16.4 (18 of 110)
Olecranon enthesophyte	11.8 (13 of 110)
Coronoid process osteophyte	10.9 (12 of 110)
Medial epicondyle enthesophyte	9.1 (10 of 110)
Medial epicondyle soft-tissue calcification	0.9 (1 of 110)

Table III Strengths of associations between studied variables and calcifications in lateral epicondylitis patients in univariate analysis

Studied variable	Overall calcification		Enthesophyte		Soft-tissue calcification	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.07 (0.99-1.08)	.095	1.02 (0.97-1.07)	.449	1.04 (0.98-1.10)	.172
Sex	0.77 (0.35-1.69)	.507	1.16 (0.43-3.13)	.775	0.47 (0.16-1.40)	.176
BMI	1.03 (0.93-1.14)	.563	1.05 (0.92-1.20)	.445	1.00 (0.88-1.13)	.967
Dominant-side involvement	1.07 (0.41-2.79)	.888	2.91 (0.63-13.55)	.173	0.49 (0.16-1.47)	.202
Occupation						
Office worker	1.00 (reference)	.948	1.00 (reference)	.869	1.00 (reference)	.627
Manual laborer	0.85 (0.32-2.25)	.744	1.40 (0.40-4.98)	.601	0.56 (0.17-1.86)	.342
Housewife	0.89 (0.31-2.59)	.832	1.33 (0.33-5.30)	.689	0.65 (0.17-2.42)	.519
Symptom duration	1.01 (1.00-1.02)	.209	1.01 (1.00-1.02)	.119	1.00 (0.98-1.02)	.958
Hand-grip power	0.99 (0.97-1.00)	.126	0.99 (0.97-1.01)	.381	0.99 (0.97-1.01)	.286
VAS pain score	1.42 (1.12-1.79)	.004	1.21 (0.93-1.57)	.159	1.43 (1.06-1.93)	.020
Stretching exercise	2.00 (0.80-5.00)	.141	2.40 (0.79-7.31)	.123	2.20 (0.58-8.38)	.248
ESWT	0.86 (0.33-2.23)	.761	1.08 (0.34-3.40)	.898	0.65 (0.17-2.51)	.529
History of steroid injection	3.70 (1.57-8.75)	.003	1.37 (0.51-3.68)	.529	9.12 (1.98-41.93)	.005
With local anesthetic	1.17 (0.51-2.65)	.713	1.03 (0.37-2.83)	.962	0.94 (0.32-2.73)	.906
Without local anesthetic	5.42 (1.95-15.04)	.001	1.54 (0.49-4.86)	.460	9.21 (2.99-28.29)	<.001
No. of steroid injections	1.16 (1.04-1.28)	.006	1.02 (0.92-1.13)	.750	1.18 (1.06-1.32)	.002
With local anesthetic	1.57 (1.21-2.03)	.001	1.11 (0.94-1.33)	.229	1.24 (1.04-1.47)	.016
Without local anesthetic	1.95 (1.27-2.98)	.002	1.04 (0.85-1.28)	.706	1.70 (1.34-2.15)	<.001

OR, odds ratio; *CI*, confidence interval; *BMI*, body mass index; *VAS*, visual analog scale; *ESWT*, extracorporeal shockwave therapy.

Table IV Strengths of associations between studied variables and calcification, in multivariable analyses

Studied variables	Overall calcification				Soft-tissue calcification			
	OR (95% CI)	*P* value	VIF	Condition index	OR (95% CI)	*P* value	VIF	Condition index
Pain VAS	1.33 (1.04-1.70)	.025	1.062	7.605	1.32 (0.97-1.80)	.079	1.047	7.215
History of steroid injection	3.27 (1.35-7.93)	.009			7.63 (1.63-35.72)	.010		
Pain VAS	1.31 (1.02-1.68)	.033	1.098	7.461	1.28 (0.93-1.76)	.125	1.083	7.060
Number of steroid injections	1.13 (1.02-1.26)	.025			1.18 (1.06-1.32)	.002		

OR, odds ratio; *CI*, confidence interval; *VIF*, variance inflation factor; *VAS*, visual analog scale.

associated with soft-tissue calcification. The ORs with 95% CIs for all variables are summarized in Table IV.

Discussion

This study found that the prevalence of overall calcification in LE was 34.6%; enthesophytes and soft-tissue calcification constituted 18.2% and 16.4%, respectively. This study also found that soft-tissue calcification was significantly associated with steroid injections.

Several studies have reported the prevalence of calcifications around the lateral epicondyle in LE. Nirschl[15] reported that 22% of LE patients had calcifications with some form of "bony exostosis" at the tip of the lateral epicondyle, which is similar to the prevalence of enthesophytes found in our study. However, that study reported that soft-tissue calcification located at the common extensor tendon just distal to the lateral epicondyle was rarely observed, which differs from our study's finding. Pomerance[17] reported a 7% prevalence of calcification in LE. That study did not distinguish enthesophytes from soft-tissue calcification and did not determine any association between steroid injection and calcification. Shillito et al[19] reported a 47% prevalence of calcifications around lateral epicondyles, classifying the calcifications as enthesophytes (44%) or soft-tissue calcifications (3%). That study reported no significant differences in prior steroid injection, VAS pain score, and QuickDASH (short version of Disabilities of the Arm, Shoulder and Hand questionnaire) score between patients with and without calcifications. Our study found a relatively higher prevalence of soft-tissue calcification (16%) than their study (3%). Those differences might arise from differences in the study populations. A history of steroid injection was present in 53% of patients in our study population compared with 7% in the study of Shillito et al. On the basis of our study's finding that soft-tissue calcification is associated with steroid injection, a higher prevalence of soft-tissue calcifications can be explained by a higher prevalence

of prior steroid injections. Because the study of Shillito et al had a low prevalence of soft-tissue calcification, they did not evaluate soft-tissue calcifications separately from overall calcifications, and this led to the failure in finding statistically significant factors between patients with and without calcifications. Zhu et al[24] reported the prevalence of soft-tissue calcification as 40.8%. Among their patients, 61.8% had received physical and/or block therapy, but their report did not specify the percentage of patients with soft-tissue calcification who received steroid injections as block therapy.

One possible theory regarding the pathogenesis of soft-tissue calcification is that local tissue damage, which leads to the release of alkaline phosphatase with increased local tissue pH, results in calcium salt precipitation in soft tissue.[2] In plantar fasciitis and LE, soft-tissue calcification with no definite pathogenesis has been reported as a complication after steroid injection.[7,10] Previous studies have suggested 2 possible mechanisms through which steroid injections cause soft-tissue calcification. The first is related to adjusted materials in the solvent,[10] and the second involves an accumulation of insoluble steroid.[7] Friemann et al[10] suggested that the calcifying necrosis of collagen fibers might have been induced by soybean oil, which was used as a carrier of dexamethasone. Conti and Shinder[7] suggested that the accumulation of insoluble steroid acts as a foreign body and induces a chronic granulomatous inflammatory process, which subsequently induces soft-tissue calcification. An additional possibility regarding the pathogenesis of soft-tissue calcification is the role of local anesthetics. One study reported that amino-amide local anesthetics may be harmful to tendon cells.[21] We could not find any significant association between soft-tissue calcification and a history of steroid injection in conjunction with use of a local anesthetic, but we found an association between soft-tissue calcification and the number of steroid injections in conjunction with a local anesthetic. In addition, the prevalence of soft-tissue calcification was higher in patients who had been treated with steroid injection alone than in patients who had been treated with steroid injection in conjunction with use of a local anesthetic. This finding suggests that soft-tissue calcification is significantly associated with steroid injection rather than with a local anesthetic. Further study is necessary to clarify whether a local anesthetic alone should be used in such patients.

Nirschl[15,16] reported the clinical significance of soft-tissue calcification as a factor in deciding the surgical treatment of LE. He suggested that tendon calcification represents a pathologic tendon and may be refractory to conservative treatment. In our study, the VAS pain score was significantly associated with overall calcification and with soft-tissue calcification, not with enthesophytes. This means that the pain of patients who had soft-tissue calcification was more severe than the pain of patients who had enthesophytes. This finding supports Nirschl's previous studies' finding. In our study, 7 patients received surgical treatment. Of these patients, 6 (85.7%) had been treated with steroid injection and 4 (57.1%) had soft-tissue calcification. The sample size of surgically treated patients was too small and the follow-up period of conservatively treated patients was too short to allow us to statistically determine the association between the soft-tissue calcification and clinical outcomes. Therefore, further study is necessary to investigate the clinical significance of soft-tissue calcification.

This study has several limitations. We did not perform any tests to validate the interobserver reliability of the diagnosis of LE. However, such a diagnosis is a common event that reflects daily clinical practice. Therefore, this study's result has clinical significance despite its possible limitations in diagnostic accuracy. We could not evaluate whether the presence of soft-tissue calcification affected clinical results. Because triamcinolone was used in all steroid injections, we could not determine whether the association between steroid injection and soft-tissue calcification was a common effect of steroid or a limited effect of triamcinolone. We suggest that steroid injection is a significantly associated factor for soft-tissue calcification in LE. However, whether steroid injection is a cause or cofactor of soft-tissue calcification in LE must be determined in a future study with a larger study population and additional studied variables.

Conclusion

The significant association of steroid injections with soft-tissue calcification in LE suggests that this calcification is likely to be an iatrogenic complication of steroid injection.

Disclaimer

The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

References

1. Allander E. Prevalence, incidence, and remission rates of some common rheumatic diseases or syndromes. Scand J Rheumatol 1974;3:145-53.
2. Anderson HC. Calcification processes. Pathol Annu 1980;15:45-75.
3. Assendelft WJ, Hay EM, Adshead R, Bouter LM. Corticosteroid injections for lateral epicondylitis: a systematic overview. Br J Gen Pract 1996;46:209-16.
4. Belsley DA, Kuh E, Welsch RE. Regression diagnostics: identifying influential data and sources of collinearity. Hoboken, NJ: Wiley; 2005.
5. Chard MD, Hazleman BL. Tennis elbow—a reappraisal. Br J Rheumatol 1989;28:186-90.
6. Chop WMJ. Tennis elbow. Postgrad Med 1989;86:301-4, 307-8.
7. Conti RJ, Shinder M. Soft tissue calcifications induced by local corticosteroid injection. J Foot Surg 1991;30:34-7.
8. Fess EE. Grip strength. In: Casanova JS, editor. Clinical assessment recommendations. 2nd ed. Chicago: American Society of Hand Therapists; 1992. p. 41-5.

9. Fox TP, Oliver G, Wek C, Hester T. Plantar fascia calcification a sequelae of corticosteroid injection in the treatment of recalcitrant plantar fasciitis. BMJ Case Rep 2013;2013:bcr2013200303. http://dx.doi.org/10.1136/bcr-2013-200303
10. Friemann J, Mogilevski G, Höhr D, Rosorius H. Calcifying granulomatous peritendinitis after local dexamethasone treatment. Pathologe 1997;18:459-62.
11. Hamilton PG. The prevalence of humeral epicondylitis: a survey in general practice. J R Coll Gen Pract 1986;36:464-5.
12. Hsu SH, Moen TC, Levine WN, Ahmad CS. Physical examination of the athlete's elbow. Am J Sports Med 2012;40:699-708. http://dx.doi.org/10.1177/0363546511428869
13. Leclerc A, Landre M-F, Chastang J-F, Niedhammer I, Roquelaure Y. Upper-limb disorders in repetitive work. Scand J Work Environ Health 2001;27:268-78.
14. Morrey BF, Sotelo JS, Morrey ME. Morrey's the elbow and its disorders. Amsterdam: Elsevier; 2017.
15. Nirschl RP. The etiology and treatment of tennis elbow. J Sports Med 1974;2:308-23.
16. Nirschl RP. Elbow tendinosis/tennis elbow. Clin Sports Med 1992;11:851-70.
17. Pomerance J. Radiographic analysis of lateral epicondylitis. J Shoulder Elbow Surg 2002;11:156-7. https://doi.org/10.1067/mpn.2002.121147
18. Raghavendran RR, Peart F, Grindulis KA. Subcutaneous calcification following injection of triamcinolone hexacetonide for plantar fasciitis. Rheumatology (Oxford) 2008;47:1838. http://dx.doi.org/10.1093/rheumatology/ken375
19. Shillito M, Soong M, Martin N. Radiographic and clinical analysis of lateral epicondylitis. J Hand Surg Am 2017;42:436-42. http://dx.doi.org/10.1016/j.jhsa.2017.03.016
20. Shiri R, Viikari-Juntura E, Varonen H, Heliövaara M. Prevalence and determinants of lateral and medial epicondylitis: a population study. Am J Epidemiol 2006;164:1065-74. http://dx.doi.org/10.1093/aje/kwj325
21. Sung CM, Hah YS, Kim JS, Nam JB, Kim RJ, Lee SJ, et al. Cytotoxic effects of ropivacaine, bupivacaine, and lidocaine on rotator cuff tenofibroblasts. Am J Sports Med 2014;42:2888-96. http://dx.doi.org/10.1177/0363546514550991
22. Verhaar JA. Tennis elbow [thesis]. Maastricht, The Netherlands: State University of Limburg; 1992.
23. Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. Arthritis Rheum 2004;51:642-51. http://dx.doi.org/10.1002/art.20535
24. Zhu J, Hu B, Xing C, Li J. Ultrasound-guided, minimally invasive, percutaneous needle puncture treatment for tennis elbow. Adv Ther 2008;25:1031-6. http://dx.doi.org/10.1007/s12325-008-0099-6